I. Scientific Abstract

This is a pilot trial to investigate the use of intratumoral IL-12 plasmid electroporation as a method for local control and as an immunotherapy for patients with metastatic melanoma. The objective of this study is to determine the safety and efficacy of human IL-12 gene electroporation in AJCC stage IIIB, IIIC and IV melanoma. Patients treated in this study will have visible and palpable subcutaneous nodules. We will assess whether IL-12 DNA electroporation is safe and generates a cytokine and immune response locally and regression of tumor nodules into which the electroporation is administered.

In the Dose Ranging part of the study, cohorts of 3 patients will be treated at increasing dose levels of IL-12 DNA delivered by electroporation intratumorally (200, 500, 1000, 2000 or 4000 μg), on day 1 followed by the same dose on days 5 and 8. Patients will be treated at up to 5 tumor sites for a total treated tumor volume of 2 cm3. The electroporation site will be sampled by fine needle aspiration (FNA) biopsy of the tumor nodule prior to treatment and again on day 15, day 29, and day 43. After the last FNA all electroporation sites will be excised and examined for expression of IL-12 and IFN γ. The FNA sample will be also used to quantitate levels of IL-12 and IFN γ by ELISA.

In addition to evaluation of the electroporation site, pharmacokinetic studies will also be performed during this trial. Blood will be drawn before and after each electroporation (days 1, 5 and 8) and on days 15, 29 and 43 to determine if systemic IL-12 and IFN-γ levels are increased. Patients' peripheral blood mononuclear cells will be collected in order to measure the T cell responses in patients who are HLA-A2 positive. Toxicity will be assessed during this part of the study, although we do not expect to achieve a dose limiting toxicity (DLT). In the absence of a DLT, tumor regression will be used to guide selection of maximum tolerated dose (MTD). If we do not observe a dose-response for tumor regression or T cell responses, an additional 3 patients will be entered at the highest dose. If DLT is observed a classic Phase I dose escalation scheme will be used to more closely define toxicity and reach a recommended dose for Phase II study